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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/808,827	02/28/97	GUNZBURG W	GSF97-01A

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EXAMINER	
BRUSCA, J	
ART UNIT	**PAPER NUMBER**
1636	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/808,827	Applicant(s) Gunzburg et al.
	Examiner John S. Brusca	Group Art Unit 1636

☒ Responsive to communication(s) filed on *5/10/99 and 7/16/99* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 5, 7, 9-26, 28, 29, 31, and 32* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 5, 7, 9-26, 28, 29, 31, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7/16/99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/808827 is acceptable and a CPA has been established. An action on the CPA follows.

2. The amendments received 5/10/99 and 7/16/99 have been entered.

Priority

3. The receipt of the certified copy of the Danish priority paper Application No. 1017/94 and International Application No. PCT/EP95/03445 is acknowledged. It is brought to the Applicant's attention that while the International application may be claimed under 35 U.S.C. § 119, in order to establish a chain of copendency with the Danish Application, the International Application must be claimed under 35 U.S.C. § 120. The claim for domestic priority for the International Application is defective as noted in the next paragraph. It is further brought to the Applicant's attention that if the International Application is claimed under both 35 U.S.C. §§ 119 and 120, there is no effect for the claim under 35 U.S.C. § 119 because the foreign filing date of the International Application would be the same as the effective U.S. filing date. It is suggested that the substitute Rule 63 Declaration required below not claim the International Application under 35 U.S.C. § 119 to clarify this situation.

Oath/Declaration

4. The substitute declaration received 7/16/99 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

5. The instant application is a continuation-in-part of International Application No. PCT/EP85/03445. The Applicants have claimed priority to the International Application under 35 U.S.C. § 120 by the cross-reference in the first sentence of the specification. As such, the Rule 63 Declaration must acknowledge the duty to disclose information as discussed above.

Claim Objections

6. The objection to claims 22-24 and 30 in the Office Action mailed 11/9/98 is withdrawn in view of the Amendment received 5/10/99.

7. Claim 16 is objected to because of the following informalities:

Claim 16 recites "said regulatory elements are" and should be amended to recite "said regulatory element is."

Appropriate correction is required.

8. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 requires the U3 region to comprise a regulatory element, while claim 1 requires the U3 region to comprise a promoter. Therefore claim 5 does not further limit claim 1.

Claim Rejections - 35 USC § 112

9. The rejection of claims 1, 5, 7-26, and 28-30 under 35 U.S.C. § 112, second paragraph in the Office Action mailed 11/9/98 is withdrawn in view of the Amendments received 5/10/99 and 7/16/99.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 5, 7, 8-19-26, 29, 29, 31, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 7, 8-26, 28 29, 31, and 32 are indefinite for recitation of the phrase "a heterologous promoter not related to the retroviral vector" because a vector cannot comprise a

promoter not related to the same vector since the vector comprises the promoter. The rejection would be overcome by amending claims 1, 17, and 28 to delete the phrase "not related to the retroviral vector.

12. Claims 1, 5, 7, 8-26, 28 29, 31, and 32 recite the limitation "the target cell". There is insufficient antecedent basis for this limitation in the claims. . The rejection would be overcome by amending claims 1, 17, and 28 to recite "a target cell."

13. Claims 1, 5, 7, 8-26, 28 29, 31, and 32 recite the limitation "at least one of the coding sequences being inserted into the body of the vector." There is insufficient antecedent basis for this limitation in the claims. . The rejection would be overcome by amending claims 1, 17, and 28 to recite "said one or more sequences selected from coding and non-coding sequences."

14. Claims 1, 5, 7, 8-26, 28 29, 31, and 32 recite the limitation that the 3' end of the vector comprises "a partially deleted U3 region wherein said partially deleted U3 region comprises a heterologous promoter." It is not clear whether the vector comprises a heterologous promoter or the region that has been deleted comprised a heterologous promoter. The rejection would be overcome by amending claims 1, 17, and 18 to clearly state that the 3' U3 region comprises a heterologous promoter.

15. Claims 7 recites the limitation "the regulatory elements and promoters" and claims 8 and 32 recite the limitation "said regulatory elements and promoters." There is insufficient antecedent basis for this limitation in the claims. The rejection would be overcome by amending claims 7, 8, and 32 to recite "said regulatory element."

16. Claim 10 is indefinite for recitation of the phrase "based on a BAG vector" because it is not clear what "based on" means relative to a vector. The rejection would be overcome by amending claim 10 to recite "derived from a BAG vector."

17. Claims 11 and 12 recite the limitation "said coding sequence." There is insufficient antecedent basis for this limitation in the claim. The rejection would be overcome by amending claim 11 to recite "the coding sequence."

18. Claims 20 and 21 are indefinite because it is not clear whether the claims read on introduction of a retroviral vector into an animal. The rejection would be overcome by amending claim 20 to delete the phrase "target human or animal cell populations comprising cells of a human or an animal" and substituting the phrase "a human or an animal."

19. For the purpose of examination, the claims have been assumed to incorporate the suggested amendments.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Couture et al.

Claim 1 is drawn to a retroviral vector comprising a substitution of a portion of the 3' U3 region with a heterologous promoter. Claim 5 does not further limit claim 1. Claim 8 is drawn to the vector of claim 5 further limited to regulatory elements and promoters that regulate the expression of a coding sequence of the vector. Claim 9 is drawn to the retroviral vector of claim 1 further limited to an LTR derived from a virus selected from the group consisting of murine leukemia virus, mouse mammary tumor virus, Murine sarcoma virus, simian immunodeficiency virus, human immunodeficiency virus, human T cell leukemia virus, feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, and mason-pfizer monkey virus. Claim 11 is drawn to the retroviral vector of claim 1 further limited to comprise a coding sequence consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, or cytokine genes. Claim 12 is drawn to the vector of claim 11 further limited to a marker or therapeutic gene selected from the group consisting of beta-galactosidase gene, neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosine deaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guanine phosphoribosyl transferase gene, alcohol dehydrogenase gene, and hypoxanthine phosphoribosyl transferase gene. Claim 15 is drawn to the vector of claim 1 comprising a DNA fragment homologous to a cellular sequence. Claim 16 is drawn to the vector of claim 5 further limited to regulatory elements regulatable by trans acting molecules. Claim 17 is drawn

to a kit comprising the retroviral vector of claim 1 and a packaging cell line that packages the vector of claim 1. Claim 18 is drawn to the kit of claim 17 further limited to a packaging cell line that expresses retroviral proteins not expressed by the vector of the kit. Claim 19 is drawn to the kit of claim 17 further limited to a packaging cell selected from the group consisting of psi-2, psi-crypt, psi-AM, GP+E86, PA317, and GP+envAM-12. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in humans or animals or cultured cells of humans or animals. Claim 21 is drawn to the method of claim 20 further limited to comprise genes, regulatory sequences, or promoters. Claim 22 is drawn to a retrovirus produced by the kit of claim 17. Claim 23 is drawn to a retroviral provirus produced by infecting cells with the retrovirus of claim 22. Claim 24 is drawn to mRNA of the provirus of claim 23. Claim 25 is drawn to RNA of the retrovirus of claim 1. Claim 28 is drawn to a packaging cell. Claim 29 is drawn to the retrovirus produced by the vector of claim 1. Claim 31 is drawn to the vector of claim 1 further limited to comprise a promoter that is target cell specific. Claim 32 is drawn to the vector of claim 5 further limited to comprise a target cell specific promoter.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene and a neomycin resistance gene, which are considered to be cellular sequences. Couture et al. shows in the

abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors.

Therefore, Couture et al. anticipates the claimed invention.

22. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Couture et al. in light of Miller et al. and Panganiban et al. '84 cited in the Form PTO 892 in the Office Action mailed 3/16/98).

Claim 13 is drawn to the vector of claim 1 comprising an altered retroviral gene. Claim 14 is drawn to the vector of claim 1 comprising an altered or partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of Couture et al. inherently anticipate the claimed invention.

Claim Rejections - 35 USC § 103

23. The rejection of claims 1, 5, 7-9, 11-13, 16-25, and 28-30 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. is withdrawn in view of the Amendments received 5/10/99 and 7/16/99.

24. The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above, and further in view of Price et al. is withdrawn in view of the Amendments received 5/10/99 and 7/16/99.

25. The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above, and further in view of Panganiban et al. '84 in view of Scarpa et al. is withdrawn in view of the Amendments received 5/10/99 and 7/16/99.

26. The rejection of claims 15 and 26 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9,

11-13, 16-25, and 28-30 above, and further in view of Longmore et al. in view of Kay et al. is withdrawn in view of the Amendments received 5/10/99 and 7/16/99.

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

28. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Price et al. (cited in the Form PTO 892 in the Office Action mailed 3/16/98).

Claim 10 is drawn to the vector of claim 1 further limited to a vector derived from a BAG vector.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding

region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene and a neomycin resistance gene, which are considered to be cellular sequences. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

29. Claims 15, 20, 21, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Longmore et al. and Kay et al. (both cited in the Form PTO 892 in the Office Action mailed 3/16/98.

Claim 15 is drawn to the vector of claim 1 comprising a DNA fragment homologous to a cellular sequence. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in humans or animals or cultured cells of humans or animals. Claim 21 is drawn to the method of claim 20 further limited to comprise genes, regulatory sequences, or promoters. Claim 26 is drawn to a pharmaceutical comprising the retrovirus of claim 22.

Couture et al. has been summarized above.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal. Regarding the

limitation in claim 15 to a vector comprising a DNA fragment homologous to a cellular sequence, the erythropoietin receptor gene of Longmore et al. or the factor IX gene of Kay et al. teach such a sequence in a retroviral vector.

30. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Mee et al. (cited in the Form 892 in the Office Action mailed 3/16/98.

Claim 7 is drawn to the vector of claim 5 further limited to a target sell specific regulatory element and promoter selected from the group consisting of Whey Acidic Protein specific regulatory elements and promoters, Mouse Mammary Tumor Virus specific regulatory elements and promoters, beta lactoglobulin and casein specific regulatory elements and promoters, pancreas specific regulatory elements and promoters, lymphocyte specific regulatory elements and promoters, and mouse mammary tumor virus specific regulatory elements and promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland.

Couture et al. has been summarized above.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. by insertion of a promoter region in

a deleted 3' U3 region of a retroviral vector results in the expression of vector genes under the control of the inserted promoter in a cell type specific manner because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

Conclusion

31. Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. For routine submissions the FAX number is (703) 308-4242. For FAX transmissions in cases in which the Examiner has been notified by phone to expect the transmission, the FAX number is (703) 305-7939. In such cases please call the Examiner at (703) 308-4231 at the time of transmission to expedite delivery of the fax. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6 (d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, Ph.D., can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John S. Brusca, Ph.D.

Primary Examiner